IN BRIEF

PARKINSON DISEASE

Parkinson disease gene therapy rewires brain circuits to improve motor function

Previously, a phase II clinical trial demonstrated that delivery of glutamic acid decarboxylase (GAD) into the subthalamic nucleus (STN) via gene therapy led to functional improvements that lasted for 1 year in patients with Parkinson disease (PD). Researchers believed that the therapy worked by inducing an inhibitory phenotype in some neurons within the STN that prevented pathological overactivation of this area, but the exact mechanism was unknown. In a new study, the same team has performed metabolic network analysis on PET scans from 15 patients with PD who received the GAD gene therapy and 20 who had sham surgery. Patients treated with the gene therapy formed unconventional brain circuits that linked the STN to cortical motor regions. Presence of the new network pattern was associated with motor improvements. This rewiring might compensate for pathology in conventional motor circuits in PD. Formation of the new network might also be a useful biomarker in future clinical trials.

ORIGINAL ARTICLE Niethammer, M. et al. Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity. *Sci. Transl Med.* **10**, eaau0713 (2018)

DEMENTIA

Sleep deprivation promotes tauopathy in mice

A new study in mice has shown that chronic sleep disruption accelerates the progression of tau pathology, a hallmark of Alzheimer disease and frontotemporal dementia. Researchers examined the effect of chronic short sleep in mice with a Pro301Ser mutation in *MAPT* (which encodes tau) that is associated with tauopathy in humans. Chronic short sleep in early adulthood hastened the development of motor impairment, increased the rate of neuronal loss and raised the levels of pathogenic tau oligomers in the mice. The increased levels of tau oligomers were sustained after sleep disruption ceased, even after a 6-month recovery period. The results mirror previous findings that amyloid-β levels and plaque burden are increased by sleep loss in mice, and suggest that sleep habits in early life affect subsequent neurodegeneration.

ORIGINAL ARTICLE Zhu, Y. et al. Chronic sleep disruption advances the temporal progression of tauopathy in P301S mutant mice. *J. Neurosci.* **38**, 10255–10270 (2018)

NEURAL REPAIR AND REHABILITATION

Intraneuronal implants enable long-term tactile sensation in patients with hand amputation

Hand prostheses are becoming increasingly sophisticated and can perform highly dexterous motor actions. However, generation of effective sensory feedback that enables users to move and apply force with sufficient precision to perform everyday tasks remains a challenge. A new report shows that intraneuronal implantation of electrodes into the median and ulnar nerves could present a viable solution for sensory feedback. Electrical stimulation was generated by artificial sensors in a prosthesis and transmitted through electrodes implanted in three patients with transradial amputation. The patients were able to use this sensory feedback to perform delicate motor tasks such as picking up eggs. Participants also reported decreased phantom limb pain and improved mood by the end of the 6-month study. The team suggests that this approach should now be tested in a larger patient cohort.

ORIGINAL ARTICLE Petrini, F. M. et al. Six-months assessment of a hand prosthesis with intraneural tactile feedback. *Ann. Neurol.* https://doi.org/10.1002/ana.25384 (2018)

PARKINSON DISEASE

A clinically useful MRI marker of PD?

Novel processing of routine MRI scans can be used to distinguish patients with Parkinson disease (PD) from healthy controls, according to new research. The technique could provide a biomarker for PD, even at the early stages of disease.

PD is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) in the basal ganglia. Attempts to use brain imaging for early identification of this degeneration have so far been unsuccessful, and no clinically useful biomarker is currently available.

"Some MRI approaches, such as susceptibility-weighted and diffusion-weighted MRI, have shown promise in detecting PD-related changes in the SNc," says first author of the new study, Guangwei Du. "However, they are difficult to translate to a clinical setting due to their technical complexity."

Du and colleagues set out to identify an MRI marker of PD with greater translational potential. They investigated whether brain changes in PD could be identified by using T1-weighted (T1w) and T2-weighted (T2w) MRI to create T1w/T2w ratio maps. This process involves aligning identical T1w and T2w images and then dividing the value at each voxel in the T1w image by that in the equivalent voxel in the T2w image. Previous studies have suggested that the T1w/T2w ratio is sensitive to neurodegenerative changes.

The researchers created T1w/T2w ratio maps for 76 patients with PD and 70 healthy controls. The T1w/T2w ratio in the SNc was higher among patients with PD than among controls, even in patients at early stages of the disease.

These findings were validated in a second cohort of 112 patients

NEURODEVELOPMENTAL DISORDERS

New in vivo model provides insights into Down syndrome

A new study published in *Science* has shown that human neurons derived from induced pluripotent stem cells (iPSCs) can be implanted into the mouse brain to enable neuronal dynamics to be studied. With this model, researchers were able to demonstrate defects in synaptogenesis and neural network function in iPSC-derived cortical tissue grafts from individuals with Down syndrome.

Down syndrome is a multisystem disorder caused by trisomy of chromosome 21 and is believed to be the most common genetic cause of intellectual disability worldwide. Cognitive impairments are evident throughout life and, as highlighted in a recent report in *JAMA Neurology*, nearly all adults with Down syndrome eventually develop dementia. Understanding the effects of trisomy 21 on neuronal development and function could be crucial for devising new treatment strategies for this condition.

"Very little is known about the dynamics of human synaptic network development and their relevance to human diseases," says Vincenzo De Paola at Imperial College London, UK, who co-led the new study. "To address this important issue, we teamed up with Frederick Livesey's team at the Gurdon Institute in Cambridge, who had developed beautiful human cortical neurons from iPSCs."

The investigators obtained skin fibroblasts from individuals with Down syndrome and healthy controls. The cells were reprogrammed in vitro to form iPSCs, which were then differentiated into cortical neurons. These neurons were labelled with fluorescent proteins and transplanted into the brains of mice, where they were monitored longitudinally using multiphoton imaging.